RESEARCH CONSENT FORM

Providence VA Medical Center

IRB # 00001402

Subject Name: **Date:**

Title of Study: Rhode Island Diastolic Dysfunction (RIDD – HF)

Principal Investigator: Wen-Chih Wu, MD

Study Sponsor (if applicable):

1. Purpose of study and how long it will last:

This is a research study that is funded by the Veterans Administration. The medication in this study is being provided by BioMarin. The research staff will explain this study to you. Research studies include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor or other research staff to better explain the study. If you decide to participate in this study, you will be asked to sign and date this form. You are not required to take part in this study and if you choose not to participate in the study, you will not be penalized in any way.

You are being asked to be in this study because you have been diagnosed with diastolic heart failure (heart failure caused by the inability of your heart to relax properly). The study will test how well Kuvan® works to treat diastolic heart failure. Kuvan® is a synthetic form of a natural substance (BH4) produced in your body. Kuvan is already approved by the U.S. Food and Drug Administration (FDA) to treat patients with a genetic disorder called phenylketonuria. The purpose of this study is to determine whether Kuvan® improves the signs and symptoms of heart failure in patients with diastolic heart failure. You will receive physical exams and imaging procedures as part of the research study. The details of these procedures will be explained later on in this form.

This study is being conducted by Dr. Wen-Chih Wu at the Providence VAMC- We plan to enroll 30 patients. You will be in the study for approximately seven months.

2. Description of the study including procedures to be used:

We estimate that all the testing listed below will take approximately ten hours to complete, divided over the course of six months. You will have 7 clinic visits and 5 phone visits.

When all baseline tests are complete, you will be assigned at random (like flipping a coin) to one of two groups of patients. Your chance of starting in the group that takes Kuvan® is 50/50, which is the same chance of you starting in the group that does not take any medication. Group 1 will take a weight based dose (10mg/kg) for one week and then increase the dose (to 20mg/kg) for three months. Following three months they will be taken off medication for the remainder of the study. Group 2 will remain on their current medications for the first three months of the study. This group will then be started on a weight based dose of medication (10mg/kg) for one week, which will then be increased (to 20mg/kg) if the dose is tolerated. Group 2 will remain on this medication until the end of this study. During the course of this time period, you will be evaluated in clinic at six weeks and at the end of three months. You will also receive telephone calls at one, three, and nine weeks to see how you are doing and monitor the effect of the medication. During this time period, you will be evaluated in clinic at nineteen weeks and at the end of six months. You will also receive telephone calls at sixteen and twenty-two weeks.

At each visit you will be asked about your medical history and a physical examination will be performed. A member of the study team will review how well you took the study drug since your last visit. You will be asked to fill out a short questionnaire to find out how you are feeling and about your daily activities at your first visit at the end of three months and at the end of six months.

Several other procedures will be done during the six month study. You will be asked to provide a blood sample three times. You will do a bicycle exercise test three times to see how well your heart and lungs function during exercise and have an echocardiogram (harmless sound waves) to see how well your heart functions.

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STUDY PROCEDURES

Visit #1 Screening visit

The study will be explained to you and you will be able to ask questions. If you agree to participate in the study, you will be asked to sign this form, which is called an informed consent form. You will have a blood sample taken from a vein in your arm (about one-two tablespoons), fill out a short questionnaire, and you will receive a test dose of the study medication. Your blood pressure will be measured ever thirty minutes for one hour to ensure that your blood pressure is not negatively affected by the medication. If you do not have any negative effect from the test dose, you will also receive an echocardiogram (an ultrasound of your heart). If you are female, you will have a pregnancy test done. All information about you that is recorded by the study staff throughout this study will remain completely confidential. This visit is expected to last about two hours.

Visit #2 Baseline visit

You will be asked about your health, your medical history and the medications that you are taking. You will have a physical exam that includes measuring your weight and height. You will then undergo a bicycle exercise test. Next, you will be assigned to your study group. If you are assigned to group one, you will be given a three month supply of medication to take home, if you are in group two you will receive medication after three months. You will be asked to bring in the bottle with you to each study visit. This visit will last between two and three hours, depending on which group you are in.

Telephone contact Week 1

Seven days after your baseline visit, you will be called to see how you are doing and whether you are having any side effects. We will then determine whether the dose of the study drug should be increased to 20mg/kg per day.

Telephone contact Week 3

You will be called to review your level of physical exercise and whether you are having any side effects. You will be asked if you have had any Emergency Department visits or hospitalizations since your last visit.

Visit #3 Week 6

During this clinic visit you will have a brief medical history taken and physical exam. We will check your study drug use to see if you are taking it as directed. We will ask you about any changes or side effects that you may have experienced. We will ask you if you have had any Emergency Department visits or hospitalizations since your last visit. This visit is expected to last approximately thirty minutes.

Telephone contact Week 9

You will be called to review your level of physical exercise and whether you are having any side effects. You will be asked if you have had any Emergency Department visits or hospitalizations since your last visit.

Visit #4 Week 12

During this clinic visit you will complete a questionnaire, have a brief medical history and physical exam, and have your blood drawn (about two tablespoons). We will check your study medication use to see if you are taking it as directed. At this visit, you will also have an echocardiogram as well as a bicycle exercise test. We will ask you if you have had any Emergency Department visits or hospitalizations since your last visit. This visit will last about two hours. If you are in the group taking the study medication, you will be asked to stop taking the medication.

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Visit #5 Week 13
At the time of this clinic visit, you will have not taken the study medication for one week (the "wash-out period"). You will be given a supply of the study drug to take home with you. You will be asked to bring in the bottle with you to each study visit. Regardless of which group you are in, you will receive a brief medical history and physical exam, and you will be asked if you have had any Emergency Department visits or hospitalizations since your last visit. This visit will last between thirty minutes.

Telephone contact Week 16
You will be called to review your level of physical exercise and whether you are having any side effects. You will be asked if you have had any Emergency Department visits or hospitalizations since your last visit.

Visit # 6 Week 19
During this clinic visit you will have a brief medical history taken and physical exam. We will check your study drug use to see if you are taking it as directed. We will ask you about any changes or side effects that you may have experienced. We will ask you if you have had any Emergency Department visits or hospitalizations since your last visit. This visit is expected to last approximately thirty minutes.

Telephone contact Week 22
You will be called to review your level of physical exercise and whether you are having any side effects. You will be asked if you have had any Emergency Department visits or hospitalizations since your last visit.

Visit #7 Week 25
During this clinic visit you will complete a questionnaire, have a brief medical history and physical exam, and have your blood drawn (about two tablespoons). We will check your study medication use to see if you are taking it as directed. At this visit, you will also have an echocardiogram as well as a bicycle exercise test. We will ask you if you have had any Emergency Department visits or hospitalizations since your last visit. This visit will last about two hours. If you are in the group taking the study medication, you will be asked to stop taking the medication.

3. Description of any procedures that may result in discomfort or inconvenience:
Some people are not comfortable answering questions about themselves; if, for any reason, you do not wish to answer specific questions or you wish to terminate the session, you will be able to do so. You may experience some minor discomfort from having your blood drawn. You may become short of breath during the bicycle exercise test, but you can end the test at any time. During the echocardiogram, you may feel a slight discomfort from the pressure of the probe on your chest.

4. Expected risks of study:
Risks associated with exercise testing
The bicycle stress test may cause shortness of breath, dizziness, faintness or falls. However, you can stop and rest whenever you need. The probability of a more serious complication such as stroke, heart attack, or death is less than 1 in 100 chances. The bicycle stress tests are supervised and you are monitored at all times by a physician.

Risks associated with blood collection
Rarely, a blood vessel from which blood was drawn may develop a blood clot. Such a clot is not serious and requires no treatment. Also, in rare cases, fainting has occurred as a result of drawing blood. You may also experience some minor

bruising or pain at the site where the blood was drawn. These risks are the same as those you get with a standard blood test.

Risks associated with echocardiogram
There are no known risks associated with this procedure.

Risks associated with the study medication
The most common risks include: headache, runny nose, stuffy nose, sore throat, diarrhea, vomiting and cough. Extremely rare side effects (<1%) include: allergic reaction, increased activity, swelling of your legs,. You will be monitored throughout the study for these side effects. Kuvan® has not been tested in pregnant women, and there may be unknown risks for pregnant women and for their developing embryo, fetus, or unborn child. If you are a woman of childbearing age, it is important that you agree to use an acceptable method of birth control. If you become pregnant or suspect pregnant during the study, please stop the study medication and contact your study doctor. The package insert for Kuvan® is included in your study package.

Risks associated with confidentiality
With any kind of research there is a very small risk that your information may no longer be protected. There is a risk that your bank account information or social security number can be stolen and misused. We will do our best to make sure that your personal information will be kept private.

Research monitoring board
A committee made up of medical people from other institutions (the Data and Safety Monitoring Board) will regularly review this research for safety purposes.

In the event of a research related injury, you should contact Wen-Chih Wu, MD, the Principal Investigator, at 401-273-7100, ext 6237, who will make sure that your personal information will be kept private.

5. Expected benefits of study:

There are no known direct benefits to you for being in this study. During the course of the study, you will receive the results of study tests. This information might be helpful for the treatment of your heart failure. If our study shows that the study drug, Kuvan, is effective in improving signs and symptoms of heart failure then you might have benefited from having received the drug during the study. Patients in the future may benefit from this research.

6. Other treatment(s) available:

If you decide not to enter this study you will not receive the study medication. You will continue to receive the care of your diastolic heart failure from your own doctor or your regular source of medical care. Kuvan® is available outside of this study. Using Kuvan® to treat diastolic heart failure is not an FDA approved indication.

7. Costs to participants and compensation:

Costs to Participants: A veteran subject will not be required to pay for medical care and services received as a subject in an approved VA research study. Some veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services (including, but not limited to, dental services, supplies, medicines, orthopedic and prosthetic appliances, and domiciliary or nursing home care) provided by the VA, that are not part of this research study.

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Compensation Offered for Participation: You will be compensated with a $25 or $50 gift card for each clinic visit, depending on the length of the visit, for your time and effort taking part in this study. These gift cards will be for an area store, such as Stop and Shop or Walmart.

8. Use of research results:

Information collected for the purpose of this research study will be kept confidential as required by law. The results of this study may be published for scientific purposes, but your records or identity will not be revealed unless required by law. Additionally, BioMarin (the company providing the medication) will have access to the results of this study. We will do our best to make sure that your personal information will be kept private. However, we cannot guarantee total privacy. All your personal identifiers will be removed and replaced with a unique identifying number. The link between your study number and your identifying information will be stored on the secure VA server in a restricted folder that only the research staff has access to. All informed consent forms will be kept in a locked office to which only the study staff has access to.

9. Right of investigator to terminate participation:

This study is expected to end after all participants have completed the follow up visits and all information has been collected. This study may be stopped at any time by your study doctor, even without your consent for the following reasons: your health or safety may be at risk; you have not been following study instructions; or due to an administrative decision of your study doctor. These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

10. Special circumstances:

Significant New Findings

If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it right away.

Participant Withdrawal

You can end your participation in this study at any time. If you decide to stop being in the study, we encourage you to talk to your study doctor and your treating doctor. Choosing to withdraw from the study will not interfere with your future care and you will not be penalized in any way.

FDA related studies involving drugs, biomedical drugs and medical devices

Federal law requires that information about this trial be submitted to a government operated clinical trial registry data bank. The registry bank provides general information about clinical trials and specific information about this trial, including results once available. It will not contain any of your personal information or any details that might identify you as a participant. The registry bank can be accessed by you and the general public at www.ClinicalTrials.gov. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

RESEARCH PARTICIPANT'S RIGHTS: I have read or have had read to me all of the above.
Dr. Wen-Chih Wu or his research staff has explained the study to me and answered all of my questions. I have been told of the risks or discomforts and possible benefits of the study. I have been told of other choices of treatment available to me.

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I have been told that I do not have to take part in this study, and my refusal to participate will involve no penalty or loss of rights to which I am entitled. I may withdraw from this study at any time without penalty or loss of VA or other benefits to which I am entitled.

The results of this study may be published, but my records will not be revealed unless required by law. The Institutional Review Board at the Providence VA Medical Center or other federal oversight offices may monitor my records for quality assurance purposes. Federal agencies including, but not limited to, the Food and Drug Administration (FDA), the Office for Human Research Protection (OHRP), the Office for Research Oversight (ORO), the Office of the Inspector General (OIG) and the Government Accounting Office (GAO) may have access to the records as allowed by law. If an FDA-regulated test article is part of this study, the FDA may choose to inspect research records that include research subject's individual medical records. Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1.

If I experience a side effect or adverse (bad or unexpected) reaction as a result of my involvement in this study, I will report these to the study investigator Dr. Wen-Chih Wu at 401-273-7100,ext 6237 who will arrange for any medical treatment that is necessary. After hours, I will call the operator who will page the cardiology fellow on call after hours at 401-273-7100,ext 0.

In case there are medical problems or questions, I have been told I can call Dr. Wen-Chih Wu at 401-273-7100,ext 6237 during the day and the operator who will page the cardiology fellow on call after hours at 401-273-7100,ext 0 after hours. If any medical problems occur in connection with this study the VA will provide emergency care.

The VA has the authority to provide medical treatment to participants (veterans and non-veterans) injured by participation in a VA study. If you are injured as a result of being in this study, the VA will provide the necessary medical treatment in accordance with federal law. If you want to make a legal claim against the VA or anyone who works for the VA, special laws may apply. The Federal Tort Claims Act (28 U.S.C. 1346(b), 2671-2680) is a federal law that controls when and how a person can bring a claim against the U.S. Government. If you sign this document you are not giving up your right to make a legal claim against the United States.

I can call the IRB Coordinator at (401) 273-7100 ext. 3470, the Research Administrative Officer at (401) 273-7100 ext. 3478 or the Providence VAMC Patient Advocate at (401) 273-7100 ext. 3093 while I am a participant or after my participation is over for the following: 1) concerns, 2) complaints, 3) problems, 4) suggestions, 5) more information, 6) questions about my rights as a research participant or 7) verifying the validity of the study and authorized contacts.

I voluntarily consent to participate in this study. I confirm that I have read this consent form or it has been read to me, and I agree it explains what this study is about and how and why it is being done. I will receive a signed copy of the consent form document after I sign it.

Participant's Signature	Participant (printed)	Date
Signature of Person Obtaining Consent	Person Obtaining Consent (printed)	Date

Version Date: ***12/13/15, 2/10/15, 11/09/15***